REMARKS

Claims 93-120 and 144-151 are pending; each of the pending claims has been rejected.

No new matter has been added. Entry of the response is respectfully requested.

I. Formal Matters

Applicants thank the Examiner for returning a signed and initialed copy of the reference list submitted with the Information Disclosure Statement in this application on October 12, 2004.

However, only the U.S. patent documents are initialed. Applicants respectfully request the Examiner to return a fully acknowledged copy of the reference list.

II. Claim Rejections Under 35 U.S.C. §103

A. At paragraph 6 of the Office Action, claims 93-97, 102-110 and 115-120 are rejected under 35 U.S.C. §103(a) as being unpatentable over Lidor (1993) or Rosenblum (1996), in view of Chari (1992).

The Examiner notes that claim 93 is drawn to a pharmaceutical composition comprising a chemotherapeutic agent and an immunoconjugate (maytansinoid linked to an antibody). The Examiner has conducted a search where the chemotherapeutic agent is cisplatin.

As to the rejection, the Examiner states that Lidor teaches a supra-additive cytotoxicity afforded by the combination of an immunotoxin (comprising an antibody and a ricin A chain) and a chemotherapeutic agent (cisplatin). The Examiner admits that Lidor does not teach an immunotoxin comprising a maytansinoid.

The Examiner further states that Rosenblum teaches that chemotherapeutic agents such as 5-FU, cisplatin, interferons alpha and gamma, and etoposide augment the cytotoxicity of an

immunotoxin comprising gelonin. The Examiner admits that Rosenblum also does not teach an immunotoxin comprising a maytansinoid.

As to Chari, the Examiner states that this document teaches immunoconjugates comprising anticancer drugs with high cytotoxicity linked to antibodies via cleavable disulfide linkages. Chari identifies maytansine as a drug having high toxicity to cancer cells.

The Examiner concludes that it would have been *prima facie* obvious to the skilled artisan to substitute a maytansinoid for the ricin A chain in the immunoconjugate of Lidor, or for the gelonin in the immunoconjugate of Rosenblum. The Examiner states that the skilled artisan would have been motivated to do so with a reasonable expectation of success by the teachings of Chari on the high therapeutic index afforded by the use of a maytansinoid conjugate because the disulfide linkers provided by Chari would be efficient at releasing the toxic maytansinoid from the antibody once internalized in a cell. The Examiner further states that the skilled artisan would expect the maytansinoid immunotoxin to have similar therapeutic potential as the ricin A immunotoxin of Lidor or the gelonin immunotoxin of Rosenblum.

Lidor

Applicants respectfully traverse the rejection of the noted claims because the Examiner has not established a *prima facie* case of obviousness with respect to Lidor and Chari. In order for the Examiner to maintain a rejection under 35 U.S.C. §103, the Examiner must establish a *prima facie* case of obviousness. That is, the Examiner must show (1) that there is a suggestion or motivation in the cited references or the general knowledge of the art to modify the references to make the claimed invention, (2) that there is a reasonable expectation of success that the modification will yield the claimed subject matter, and (3) that the references, as modified, teach

all of the claim elements. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See also MPEP §2142. Applicants respectfully contend that the Examiner has not established element (2), i.e., that there would have been a reasonable expectation of success in combining the teachings of Lidor and Chari to arrive at the invention now being claimed.

In the rejection, the Examiner states that there would have been a reasonable expectation of success in view of the teachings of Chari on the high therapeutic index afforded by the use of a maytansinoid conjugate because the disulfide linkers provided by Chari would be efficient at releasing the toxic maytansinoid from the antibody once internalized in a cell (page 5 of the office action). The Examiner also states that the skilled artisan would expect the maytansinoid immunotoxin to have similar therapeutic potential as the ricin A chain immunotoxin of Lidor.

Applicants first note that the Examiner has not provided any support for his position. Indeed, the Examiner merely assumes that because an immunoconjugate comprising an antibody linked to a maytansinoid has a high therapeutic index, the same immunoconjugate could be used in conjunction with a chemotherapeutic agent as an effective pharmaceutical composition.

For the reasons that follow, the skilled artisan would not have had a reasonable expectation of success in combining these two elements of the claims.

Applicants first offer the following comments concerning the science behind synergistic combinations. It is well known to one of ordinary skill in the art that clinical or therapeutic synergism requires a complex balance of therapeutic and toxic interactions. See *Fiorentino* abstract (cited by the examiner). Synergistic behavior between two chemotherapeutic agents is extremely unpredictable, and must be worked out experimentally for each class of chemotherapeutic agents. The reasons for this include the following. For most, if not all, classes

of chemotherapeutic agents, the actual biological mechanism, i.e., the entire pathway of action, is not known and therefore it is not known what actions contribute to the therapeutic effect. There are many possible known and unknown mechanisms. The addition of a second agent (e.g., an immunotoxin) on the same target increases the complexity of mechanisms to a degree that makes it impossible to predict the outcome, i.e., to predict if the combined effect will be synergistic, additive, or antagonistic.

More specifically, the demonstration that an antibody-ricin A chain conjugate has supra-additive cytotoxicity with cisplatin (as in Lidor) provides no insight into the potential activity of an antibody-maytansinoid conjugate in combination with cisplatin. The mechanism of action of ricin is very complex, not entirely understood, and different from the mechanism of action of maytansine, which is also complex and not entirely understood. Further, conjugation of these agents to an antibody adds another level of complexity to the mechanisms, which again will be different for different classes of agents.

Indeed, the experimental results of Lidor suggest that supra-additive cytotoxicity found therein is directly related to the cooperative effect of cisplatin and ricin. Lidor studied the effect of ricin immunotoxin alone, and in combination with cisplatin, and showed that both decreased intracellular glutathione levels and reduced glutathione-S-transferase activity. Repair of DNA damage induced by the combination of cisplatin and the ricin immunotoxin was significantly reduced when compared to repair after damage with cisplatin alone. Importantly, Lidor concluded by stating that their findings suggest ricin immunotoxins affect levels and activity of the enzymes required for the prevention and repair of cisplatin damage (page 2446, col. 1, third full paragraph). Thus, as ricin blocks the activity of the enzymes required to repair cisplatin

damage, it is clear that the supra-additive effect is very specific to these two agents. The skilled artisan would not have had a reasonable expectation that maytansine could be substituted for ricin.

Indeed, as maytansine is a mitotic inhibitor, the modes of action of ricin and maytansine are quite different. Treatment of L1210 cells *in vivo* with maytansine has been reported to result in 67% of the cells accumulating in mitosis. Untreated control cells were reported to demonstrate a mitotic index ranging from between 3.2 to 5.8% (Sieber et al., 43 *Comparative Leukemia Research* 1975, Bibl. Haemat. 495-500 (1976)). Experiments with sea urchin eggs and clam eggs have suggested that maytansine inhibits mitosis by interfering with the formation of microtubules through the inhibition of the polymerization of the microtubule protein, tubulin (Remillard et al. *Science* 189:1002-1005 (1975)).

As it is apparent that maytansine would not have the same effect on the enzymes required to repair DNA damage as does ricin, the skilled artisan would not have had a reasonable expectation of success in substituting maytansine for ricin, in combination with cisplatin. As it appears to be the combined effect of ricin and cisplatin that results in an highly effective agent, substitution of ricin for a compound (e.g., maytansine) that does not inhibit the same enzymes would instead be expected to result in a composition with diminished effectiveness.

Applicants note that in the previous Office Action, the claims were rejected in a similar manner over Seigell and Chari, where Siegell taught paclitaxel as the chemotherapeutic agent and an enodotoxin immunoconjugate, and Chari taught a maytansine immunoconjugate. In response to this rejection, Applicants argued that "there is no reasonable expectation of success for the combination of the two references due to complexity of the interaction between the

maytansinoid-immunoconjugate with the cellular machinery and the interaction between paclitaxel and the cellular machinery." In withdrawing the rejection, the Examiner states in the outstanding Office Action that Applicants' argument has been found "persuasive" (see paragraph 5).

There is little difference between the rejection of the claims over Siegall and Chari in the previous office action, and the rejection of the claims over Lidor and Chari in the outstanding Office Action. In the former combination, Siegall taught a paclitaxel chemotherapeutic agent and an enodotoxin-antibody immunoconjugate. In the latter combination, Lidor teaches a cisplatin chemotherapeutic agent and a ricin A chain-antibody immunoconjugate. As the Examiner has agreed that the complexity of interaction between "the maytansinoid-immunoconjugate with the cellular machinery and the interaction between paclitaxel and the cellular machinery" results in no reasonable expectation of success for combining Siegall and Chari, the Examiner should also agree that the complexity of interaction between the maytansinoid-immunoconjugate with the cellular machinery and the interaction between cisplatin and the cellular machinery would mean that the skilled artisan would not have a reasonable expectation of success in combining Lidor and Chari. The Examiner has not indicated any meaningful distinction between paclitaxel and cisplatin in this regard.

From the explanation set forth above, it is also evident that there exists no suggestion or motivation for a skilled artisan to combine the teachings of Lidor and Chari. The prior art cited by the Examiner does not suggest the desirability of such a modification or replacement. The law in this regard is clear, "both the suggestion and the reasonable expectation of success must

be founded in the prior art, not in the applicant's disclosure." *In re Vaeck,* 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

In view of these comments, it is clear that the skilled artisan would not have had a reasonable expectation of success in combining Lidor and Chari to arrive at the claimed invention. Nor would he have been motivated by the teachings of either document to combine the teachings to arrive at Applicants' invention. As the Examiner has not established a *prima facie* case of obviousness, the claims are patentable over the combination of Lidor and Chari. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

Rosenblum

The comments above concerning the lack of a reasonable expectation of success in combining Lidor with Chari, in view of the complexity of the interaction between the maytansinoid-immunoconjugate with the cellular machinery, and the interaction between cisplatin and the cellular machinery, apply equally well to the instant rejection.

Applicants further note that gelonin is a glycosylated type I ribosome-inactivating protein (RIP) which catalytically and irreversibly inactivates eukaryotic ribosomes. Such activity of gelonin is completely different from the mitosis inhibiting activity of maytansine. This difference in activity further adds to the complexity of interactions between the immunoconjugates, the chemotherapeutic agents, and the cellular machinery. Further, there is no teaching to suggest that gelonin could be substituted for by maytansine to produce an agent with the effectiveness of the combination of a gelonin-immunotoxin and cisplatin.

In view of the lack of a reasonable expectation of success in combining the teachings of Rosenblum and Chari, in view of the complexity of the interactions between immunotoxins and

chemotherapeutic agents, and in view of the different modes of action of gelonin and maytansine, the Examiner has not established a *prima facie* case of obviousness. The claims are thus patentable over the combination of Rosenblum and Chari. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

B. At paragraph 7 of the Office Action, claims 93-97, 99, 102-110, 112 and 115-120 are rejected under 35 U.S.C. §103(a) as being unpatentable over Lidor and Chari, or Rosenblum and Chari, as applied to claims 93-97, 102-110 and 115-120 above, and further in view of Schlom (1991).

The Examiner notes that claim 99 specifies the antibody fragments of claim 93, and claim 112 specifies the antibody fragments of the kit of claim 106. The Examiner states that Schlom teaches the advantages of antibody fragments, and asserts that it would have been *prima facie* obvious to use the antibody fragments in place of the complete antibodies in the immunoconjugates taught by Lidor or Rosenblum. The Examiner contends that the skilled artisan would have been motivated to do so by the teachings of Schlom on the improved efficacies afforded by the administration of antibody fragments versus whole antibodies.

Applicants reiterate their comments above that the Examiner has failed to establish a *prima facie* case of obviousness with regard to the combination of Lidor and Chari, or Rosenblum and Chari. In particular, the skilled artisan would not have had a reasonable expectation of success in combining cited documents to arrive at the invention now being claimed.

Schlom does not teach compositions comprising an immunotoxin and a chemotherapeutic agent. As Schlom does nothing to establish a reasonable expectation of success in combining the

teachings of the cited art, neither the combination of Lidor and Chari, or Rosenblum and Chari, in view of Schlom, makes the pending claims unpatentable. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

C. At paragraph 8 of the Office Action, claims 93-97, 99, 101-110, 112 and 114-119 are rejected under 35 U.S.C. §103(a) as being unpatentable over Lidor and Chari, or Rosenblum and Chari, as applied to claims 93-97, 102-110 and 115-120 above, and further in view of Liu (EOID, 1997) and the abstract of Fiorentino (1988) and Schlom (1991).

The Examiner notes that claims 101, 114, 144 and 146 recite specific humanized antibodies (C242 and N901), and that claims 148 and 150 recite the use of humanized antibodies.

The Examiner states that while neither Lidor and Chari, nor Rosenblum and Chari, teach the use of humanized C242-DM1 conjugates, Lidor suggests the general property of synergism between an immunotoxin and cisplatin. The Examiner further states that Liu teaches a C242-DM1 conjugate, and that Fiorentino teaches that clinical synergy is often evidenced in combinations with platinum. The Examiner notes that Schlom teaches humanization of murine antibodies to overcome the inefficiency encountered with murine antibodies due to the HAMA response.

The Examiner concludes that it would have been *prima facie* obvious to combine a humanized C242-DM1 immunotoxin with cisplatin for treatment of patients with colorectal cancer. The Examiner explains the motivation for doing so with reference to the teachings of Lidor on the general mechanisms affording synergy with combinations of immunotoxins and alkylating agents (and the further example in Rosenblum with cisplatin). The Examiner states

that the skilled artisan would have had a reasonable expectation of success as evidenced by Fiorentino which cites platinum as an agent in clinical synergistic combinations.

The Examiner goes on to state that the skilled artisan would have been motivated to make a humanized version of the C242 antibody for administration to humans. Further, one would have been motivated to make the scFv fragment of C242 for administration to humans based on the teachings of Liu regarding poor penetration of immunoconjugates into tumors, and the teachings of Schlom on the enhanced ability of scFv to penetrate tumor vasculature and the decreased HAMA response associated with antibody fragments.

Applicants note that the Examiner has extended the initial rejection of claims 93-97, 102-110 and 115-120, discussed above in section **II. A.**, to claims that recite the use of humanized antibodies. The Examiner cites to Liu, Fiorentino and Schlom as supporting the rejection.

Applicants reiterate their comments above that the Examiner has failed to establish a *prima facie* case of obviousness with regard to the combination of Lidor and Chari, or Rosenblum and Chari. In particular, the skilled artisan would not have had a reasonable expectation of success in combining the cited documents to arrive at the invention now being claimed.

None of Liu, Fiorentino and Schlom, alone or in combination, teaches or suggests the subject matter of the rejected claims. That is, none of Liu, Fiorentino and Schlom appears to teach a combination of a chemotherapeutic agent and an immunoconjugate.

Accordingly, the Examiner has not established a *prima facie* case of obviousness. In particular, for the reasons discussed above it is clear that the skilled artisan would not have had a

reasonable expectation of success in combining any of the documents cited by the Examiner to arrive at the claimed invention.

Furthermore, the Examiner states that the skilled artisan would have had a reasonable expectation that "the combination with platinum would be synergistic as evidence by the abstract of Fiorentino et al who cite platinum as an agent in clinical synergistic combinations." However, the clinical synergy that the Examiner indicates is disclosed in Fiorentino is synergy between various chemotherapeutic agents, and not synergy between a chemotherapeutic agent and an immunotoxin. Because of the complex nature between the interactions of chemotherapeutic agents and immunotoxins with the cellular machinery, as discussed above, and the fact that Fiorentino only relates to synergism between one class of compounds (chemotherapeutic agents), again it is clear that the skilled artisan would not have had a reasonable expectation of success in combining chemotherapeutic agents with immunotoxins on this basis.

As neither Lidor and Chari, nor Rosenblum and Chari, in view of Liu, Fiorentino or Schlom, establishes a reasonable expectation of success in combining the teachings of the cited art, none of the cited art makes the pending claims unpatentable. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

D. At paragraph 9 of the Office Action, claims 93-98, 100-111, 113 and 115-119 are rejected under 35 U.S.C. §103(a) as being unpatentable over Lidor and Chari, or Rosenblum and Chari, as applied to claims 93-97, 102-110 and 115-120 above, and further in view of Liu (AACR, 1997) and the abstract of Fiorentino (1988) and Schlom (1991).

The Examiner notes that claim 98 specifies that the immunoconjugate binds a CD5 antigen, claims 100 and 111 specify that the antibody in the immunoconjugate is humanized N901, and claim 111 specifies that the immunoconjugate binds to CD56.

The Examiner states that while neither Lidor and Chari, nor Rosenblum and Chari, teach the use of humanized C242-DM1 conjugates, Lidor suggests the general property of synergism between an immunotoxin and cisplatin. The Examiner further states that Liu teaches administration of an immunoconjugate comprising humanized N901 antibody and DM1, that Lynch[1] teaches that that the N901 antibody binds CD56, and that Fiorentino teaches that clinical synergy is often evidenced in combinations with platinum. The Examiner notes that Schlom teaches humanization of murine antibodies to overcome the inefficiency encountered with murine antibodies due to the HAMA response.

The Examiner concludes that it would have been *prima facie* obvious to combine a humanized N901-DM1 immunotoxin with cisplatin for treatment of patients with small cell lung cancer. The Examiner explains the motivation for doing so with reference to the teachings of Lidor on the general mechanisms affording synergy with combinations of immunotoxins and alkylating agents (and the further example in Rosenblum with cisplatin). The Examiner states that the skilled artisan would have had a reasonable expectation of success as evidenced by Fiorentino which cites platinum as an agent in clinical synergistic combinations.

The Examiner goes on to state that the skilled artisan would have been motivated to make a humanized version of the N901 antibody for administration to humans. Further, one would

---

[1] Applicants note that the Examiner has neglected to include the citation to this document in the paragraph summarizing this rejection.

have been motivated to make the scFv fragment of N901 for administration to humans based on the teachings of Liu regarding poor penetration of immunoconjugates into tumors, and the teachings of Schlom on the enhanced ability of scFv to penetrate tumor vasculature and the decreased HAMA response associated with antibody fragments.

Applicants note that the Examiner has extended the initial rejection of claims 93-97, 102-110 and 115-120, discussed above in section **II. A.**, to claims that recite the use of specific humanized antibodies and cell surface antigens. The Examiner cites to Liu, Lynch, Fiorentino and Schlom as supporting the rejection.

Applicants reiterate their comments above that the Examiner has failed to establish a *prima facie* case of obviousness with regard to the combination of Lidor and Chari, or Rosenblum and Chari. In particular, the skilled artisan would not have had a reasonable expectation of success in combining cited documents to arrive at the invention now being claimed.

None of Liu, Lynch, Fiorentino and Schlom, alone or in combination, teaches or suggests the subject matter of the rejected claims. That is, none of Liu, Lynch, Fiorentino and Schlom appears to teach a combination of a chemotherapeutic agent and an immunoconjugate.

Applicants again note that the clinical synergy that the Examiner indicates is disclosed in Fiorentino is synergy between various chemotherapeutic agents, and not synergy between a chemotherapeutic agent and an immunotoxin.

Accordingly, the Examiner has not established a *prima facie* case of obviousness. In particular, for the reasons discussed above it is clear that the skilled artisan would not have had a reasonable expectation of success in combining any of the documents cited by the Examiner to

arrive at the claimed invention. Therefore none of the cited art makes the pending claims unpatentable, and Applicants respectfully request reconsideration and withdrawal of this rejection.

III. Obviousness-type Double Patenting Rejection

At paragraph 10 of the Office Action, claims 93-97, 99, 102-110, 112 and 115-119 are rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 5,208,020 (the '020 patent) in view of Lidor.

The Examiner states that claims 1-6 of the '020 patent are drawn, in part, to cytotoxic agents comprising maytansinoids and antibodies. Claims 7-12 are drawn to pharmaceutical compositions comprising maytansinoids conjugated to antibodies. The Examiner further states that Lidor teaches supra-additive cytotoxicity afforded by the combination of an immunotoxin and cisplatin, and the advantages of using both chemotherapeutic agents and immunotoxins.

The Examiner concludes that it would have been *prima facie* obvious to include cisplatin with the pharmaceutical compositions of claims 7-12 of the '020 patent. The skilled artisan would have been motivated to do so by the teachings of Lidor on the supra-additive cytotoxicity afforded by the combination of an immunotoxin and an alkylating agent.

Applicants note that the test for obviousness-type double patenting, where the application at issue is the later filed application, is whether the invention defined in a claim in the application is an obvious variation of the invention defined in the patent (*In re Berg*, 46 USPQ2d 1226 (Fed. Cir. 1998)). It is important to note that the analysis is based on the claims of the patent itself, and not on the teachings of the specification.

Claims 7-12 of the '020 patent merely cite a pharmaceutical composition comprising a maytansinoid-based immunoconjugate. There is no recitation of a second agent in combination with the immunoconjugate, let alone a chemotherapeutic agent. As a result, it would not have been obvious to the skilled artisan to include a chemotherapeutic agent in the pharmaceutical composition of the '020 patent.

Indeed, a pharmaceutical composition comprising a chemotherapeutic agent and an immunoconjugate (as recited in the pending claims) could not be considered an obvious variation of a pharmaceutical composition solely comprising an immunoconjugate (as recited in the '020 patent). The two compositions would be expected to have very different effects *in vivo* and would be expected to be used for different purposes.

Furthermore, for the reasons discussed above, there would have been no reasonable expectation of success in combining the disclosure of Lidor with the claims of the '020 patent to arrive at the invention currently being claimed by Applicants.

Synergistic behavior between two chemotherapeutic agents is unpredictable and in each case is worked out experimentally. Reasons for this include: (a) for most, if not all, chemotherapeutic agent, the actual biological mechanism, i.e. the entire pathway of action, is not known and, therefore, it is not known what actions contribute to the therapeutic effect, (b) there are many possible known and unknown mechanisms, and (c) the addition of two agents on the same target increases the complexity of mechanisms to a degree that makes it impossible to predict the outcome, i.e., to predict if the combined effect is synergistic, additive, or antagonistic.

In view of these comments, it is clear that the cited pending claims would not be obvious in view of the claims of the '020 patent. Therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

IV. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

Drew Hissong
Registration No. 44,765

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Date: August 23, 2005